REMARKS

Claims 1-50 are pending. Claims 1-8, 11-23, 26-35 and 38-44 are under examination. Claims 1, 3, 17, 18, 22, 32 and 38 have been amended. Support for the amendments can be found throughout the specification and the claims as filed. In particular, support for the amendment can be found, for example, on page 17, lines 12-18. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Regarding the Nucleotide and Amino Acid Sequences

The Office Action has indicated that the specification contains nucleotide and/or amino acid sequences that are not identified by SEQ ID NOS. As requested by the Examiner, the specification has been amended to correspond to the Sequence Listing filed on May 28, 2002. Applicant respectfully submits that the requirements of 37 C.F.R. § 1.821 have been satisfied.

Double Patenting

Claims 1-8, 11-23, 26-35 and 38-44 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 38-44 of co-pending application serial No. 09/300,959. Applicants respectfully request that this provisional rejection be held in abeyance until there is an indication of allowable subject matter.

Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1-8, 11-23, 26-35 and 38-44 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement is respectfully traversed. Applicant respectfully submits that the specification provides sufficient description and guidance to enable the claimed methods and compositions.

Without conceding the merits of the rejection set forth in the Office Action, Applicant has nevertheless amended the claimed methods and nucleic acids to recite B cell expression elements. Claim 1, as amended, is directed to a method for stimulating an immune response, comprising administering *ex vivo* to cells from a lymphoid tissue a nucleic acid molecule comprising a B cell-specific expression element operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes, and administering B cells of the lymphoid cells to

an individual, wherein the administered B cells express the one or more heterologous epitopes and wherein expression of the one or more heterologous epitopes results in stimulation of an immune response. Claim 17, as amended, is directed to a method for stimulating an immune response, comprising administering to a lymphoid cell a nucleic acid molecule comprising a B cell-specific expression element operationally linked to a nucleic acid sequence encoding two or more heterologous epitopes, wherein the two or more heterologous epitopes are inserted within a complementarity-determining region (CDR) of an immunoglobulin molecule and are expressed in a B cell and wherein the lymphoid cell is in blood or a lymphoid tissue selected from the group consisting of lymph nodes, mucosa-associated lymphoid tissue (MALT), tonsils, Payer's patches, nasal-associated lymphoid tissue (NALT), Waldeyer's ring, and urogenital lymphoid tissue. Claim 32, as amended, is directed to a nucleic acid molecule comprising a B cell-specific expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein the heterologous polypeptide comprises two or more T cell epitopes. Claim 38, as amended, is directed to a nucleic acid molecule comprising a B cell-specific expression element operationally linked to a nucleic acid sequence encoding two or more heterologous epitopes, wherein the nucleic acid sequence encodes an immunoglobulin molecule containing the two or more epitopes and wherein the two or more epitopes are inserted within a complementarity-determining region (CDR) of the immunoglobulin molecule, wherein the heterologous epitopes comprise two or more T cell epitopes.

Applicant respectfully submits that the specification provides sufficient description and guidance to enable the claimed methods. The claims recite nucleic acids containing a B cell expression element and encoding one or more heterologous epitopes or polypeptides. Applicants respectfully submit that the alleged unpredictability asserted in the Office Action is not applicable to the claimed methods and nucleic acids which explicitly recite a nucleic acid molecule comprising a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide or one or more heterologous epitopes. The method claims further recite that the heterologous polypeptide or the one or more heterologous epitopes are expressed in a B cell. Therefore, Applicant respectfully submits that the alleged unpredictability asserted in the Office Action are not relevant to the claims specifically reciting a B cell expression element.

Applicant respectfully disagrees with the assertion in the Office Action that the specification fails to provide an enabling disclosure for the use of any route of administration or target tissue other than intrasplenic. The specification teaches that the methods of the invention can be used to deliver a nucleic acid molecule to a variety of secondary lymphoid tissues. For example, the specification teaches on page 15, lines 6-10, that a secondary lymphoid tissue target can include spleen, lymph nodes, mucosa associated lymphoid tissue, nasal associated lymphoid tissue and urogenital lymphoid tissue. Methods of administering a nucleic acid molecule are taught in the specification including, for example, on page 15, lines 2-31, which describes direct injection into lymphoid tissues such as spleen or lymph nodes. Additionally, administration by methods of *ex vivo* gene transfer to lymphoid cells is taught on page 31, line 17, to page 32, line 3, and in Example IX. Therefore, Applicant respectfully submits that the specification teaches various routes of administration.

The specification provides working examples of methods of stimulating an immune response with vectors containing B cell expression elements (see Examples). Applicant respectfully submits that the assertion in the Office Action as to whether expression in B cells alone are responsible for the observed responses or whether antigen is shed from the B cell and is picked up by other types of cells in the splenocyte population which then stimulate an immune response is not relevant to the claimed methods. The method claims recite stimulating an immune response by administering a nucleic acid molecule having a B cell expression element. Whether other cells besides B cells could contribute to the immune response is not relevant, rather, expression in B cells resulting in an immune response, as recited in the claims and demonstrated in the Examples, is what is relevant.

Applicant respectfully submits that the specification provides sufficient description and guidance for the claimed methods and nucleic acids. Accordingly, Applicant respectfully requests that this rejection be withdawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-8, 11-16 and 38-44 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. Applicant submits that the claims are clear and definite.

Claims 1-8 and 11-16 are alleged to be indefinite for omitting essential steps. Claim 1 has been amended as suggested by the Examiner to recite administering B cells of the lymphoid cells to an individual, wherein the administered B cells express one or more heterologous epitopes and wherein expression of the one or more heterologous epitopes results in stimulation of an immune response. Applicant respectfully submits that the claims are clear and definite and respectfully requests that this rejection be withdrawn.

Claims 38-44 are alleged to be indefinite for lack of antecedent basis for the term "heterologous peptide." Claim 38 has been amended to recite "heterologous epitopes" and to otherwise correct antecedent basis. Applicant respectfully submits that the claims are clear and definite and respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102

The rejection of claims 32, 33, 35, 38, 39, 41, 42 and 44 under 35 U.S.C. § 102 (b) as allegedly anticipated by Xiong et al., Nat. Biotech. 15:882-886 (1997), is respectfully traversed. Applicant respectfully submits that the claims are novel over Xiong et al.

Applicant respectfully submits that the claimed nucleic acid molecules are novel over Xiong et al. Independent claim 32, as amended, is directed to a nucleic acid molecule comprising a B cell-specific expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein the heterologous polypeptide comprises two or more T cell epitopes. Independent claim 38, as amended, is directed to a nucleic acid molecule comprising a B cell-specific expression element operationally linked to a nucleic acid sequence encoding two or more heterologous epitopes, wherein the nucleic acid sequence encodes an immunoglobulin molecule containing the two or more epitopes and wherein the two or more epitopes are inserted within a complementarity-determining region (CDR) of the immunoglobulin molecule, wherein the heterologous epitopes comprise two or more T cell epitopes.

In contrast Xiong et al., does not teach the claimed nucleic acid molecules. In particular, Xiong et al. indicates that an antigenized antibody was engineered to code for two distinct 12 amino acid long peptides representing a B cell and Th cell epitope (see page 882, paragraph

bridging first and second columns). Each of the epitopes were separately cloned into CDR2 and CDR3 (see page 885, first paragraph under "Experimental protocol"). Thus, Xiong et al. does not teach a nucleic acid molecule encoding a heterologous polypeptide comprising two or more T cell epitopes, as in claim 32, or a nucleic acid molecule encoding two or more epitopes within a CDR, as in claim 38. Absent such a teaching, Xiong et al. cannot anticipate the claimed nucleic acid molecules. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

The rejection of claims 1-8, 11-23, 26-35 and 38-44 under 35 U.S.C. § 103 as allegedly obvious over Xiong et al., supra, in view of Bona et al., U.S. Patent No. 5,969,109, and Kundig et al., U.S. 2002/0007173, is respectfully traversed. Applicant respectfully submits that the claims are unobvious over Xiong et al., alone or in combination with Bona et al. and/or Kundig et al.

With regard to nucleic acid claims 32-35 and 38-44, as discussed above, Xiong et al. does not teach or suggest a nucleic acid molecule encoding a heterologous polypeptide comprising two or more T cell epitopes or a nucleic acid molecule encoding two or more epitopes within a CDR. Furthermore, neither of Bona et al. or Kundig et al. cure the deficiencies of the claimed nucleic acids. Accordingly, Applicant respectfully submits that the claimed nucleic acid molecules are unobvious over Xiong et al., alone or in combination with Bona et al. and/or Kundig et al.

Regarding claims 1-8, these claims are directed to methods for stimulating an immune response by administering *ex vivo* to cells from a lymphoid tissue a nucleic acid molecule comprising a hematopoietic cell-specific B cell expression element operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes, and administering B cells of the lymphoid cells to an individual, wherein the administered B cells express the one or more heterologous epitopes and wherein expression of the one or more heterologous epitopes results in stimulation of an immune response. Applicant respectfully submits that none of Xiong et al., Bona et al. and/or Kundig et al. teaches or suggest stimulating an immune response by administering a nucleic acid encoding one or more heterologous epitopes to cells *ex vivo* and

administering the cells expressing one or more heterologous epitopes to an individual to stimulate an immune response.

With respect to claims 17-23 and 26-31, these claims are directed to methods for stimulating an immune response by administering to a lymphoid cell a nucleic acid molecule comprising a B cell-specific expression element operationally linked to a nucleic acid sequence encoding two or more heterologous epitopes, wherein the two or more heterologous epitopes are inserted within a CDR of an immunoglobulin molecule and wherein the lymphoid cell is in blood or a lymphoid tissue selected from the group consisting of lymph nodes, mucosa-associated lymphoid tissue (MALT), tonsils, Payer's patches, nasal-associated lymphoid tissue (NALT), Waldeyer's ring, and urogenital lymphoid tissue. Applicant respectfully submits, as discussed above, that Xiong et al. does not teach or suggest a method for stimulating an immune response using a nucleic acid molecule encoding two or more epitopes within a CDR. Furthermore, neither of Bona et al. or Kundig et al. cures the deficiencies of Xiong et al. Therefore Applicant respectfully submits that the claimed methods are unobvious over Xiong et al., alone or in combination with Bona et al. and/or Kundig et al.

Applicant respectfully submits that the claimed methods and nucleic acid molecules are unobvious over Xiong et al., alone or in combination with Bona et al. and/or Kundig et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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